Biological clocks: The coming of age

In the past several years, there has been a great deal of activity in the field of chronobiology and the impact of these developments on physiology and medicine is growing.[1,2] The understanding about the cellular basis of various body rhythms is rapidly increasing. In view of this it is relevant to take a quick over-view of biological clocks.

Life evolved on earth slowly over a few billions of years. During this time, and before, the earth has been rotating around its own tilted axis and simultaneously revolving around the sun. Thus, it is no surprise that the periodic environmental consequences of the rotation (day and night), the tilt (changing day length) and of the revolution (seasons) should influence life-forms right from their primordial beginnings.

In the background of these periodic environmental factors, it is reasonable to believe that favorable inheritable changes would have persisted. The beneficial genetic mutations expected to be selected in primitive life-forms would surely include those that led to improved survival during potentially deleterious phases of the day-night cycle or during less drastic changes induced by the changing day-length and seasons. Due to the survival benefit, these inheritable characteristics became incorporated in advanced life-forms as they evolved from simpler forms. It is only now that the underlying intracellular mechanisms involved in circadian rhythms are being discovered in many types of human cells.[2] The currently accepted defining features of circadian rhythms include the property of persistence (also described as 'self-sustaining' or 'free-running'), aperiodicity of ~24 h, entrainability by external influences (typically light), and temperature independence.

Circadian, and possibly other, rhythms in living beings could not have escaped the notice of early man. However, in the present day, the first detailed, and academic, look at these phenomena is ascribed to De Marian in the sixteenth century. This Frenchman described leaf movements in plants exposed to day and night. He also showed that these persisted even when the plants were kept indoors, protected from the variations in light.[1]

Access this article online	
Quick Response Code:	Website: www.ijabmr.org
	DOI: 10.4103/2229-516X.96788

The underlying feature of intracellular mechanisms that regulate circadian rhythms is the presence of oscillations. Feedback-based regulatory mechanisms can cause oscillations of the controlled variable if the feedback has a very high gain. It is easy to realize that any oscillatory mechanism with a periodicity of ~24 h can function as a circadian clock. In essence, these circadian clock regulators consist of genes whose transcription–translation cycles are subject to feedback from their own products. In reality, they may consist of several inter-linked regulatory genes and their products. Whatever the complexity, the underlying constant theme is an overall periodicity of ~24 h.

For over three decades the special position of the suprachiasmatic nuclei in circadian rhythms has been suspected.[3,4] So where does it fit in the scheme of things now? It is now believed that these nuclei contain several cells with their own circadian rhythms but are entrained by light via the retinal specialized ganglion cells. Neural output from the suprachiasmatic nuclei is channeled into the pineal gland and into other hypothalamic regions. Influences from these areas, humoral or neural, may ultimately help in entraining or modulating the rhythmic function of peripheral biological clocks.

One of the earliest human rhythms to be recognized was that of adrenocortical secretions.[5,6] Diurnal variations in ocular pressure and renal excretion have also been known for several years.[7] The existence of circadian rhythm in lung function meant that it was necessary that such recordings were made at the same time of the day for accuracy of comparison.[8,9]

Trends in recent years are helping to bring forth new evidence suggesting an increasing role of abnormal circadian rhythms in tissues in the pathogenesis of several types of diseases. This has been implicated in the development of obesity.[10] In a related study, it has been shown that there is circadian rhythmicity in leptin expression and also in the number of its receptors on visceral fat cells.[11] There may also be gender-specific differences in clock genes of adipose tissue.[12] This suggests that the future may show novel developments in the understanding of how obesity develops and new ways of dealing with this problem.

The cellular elements of blood also experience circadian rhythms. The expression of thrombopoietin is regulated by a cellular mechanism.[13] Besides this it has been shown that

an intrinsic cellular circadian oscillator regulates the CD4+ T cell immnune responses.[14]

A recent meta-analysis has shown that blood pressure (BP) is lowered better by antihypertensive given at bedtime than in the morning. However, this analysis failed to find conclusive evidence of reduced cardiovascular events despite the better BP control.[15] The possible link between cardiovascular events and circadian variations of blood pressure appears now to be widely accepted.

The field of chronotherapeutics that aims at tuning the administration of drugs is also expanding rapidly. It is now being recognized that maintaining a steady blood level of a drug may not always be desirable and it may be better to be in step with the biological clocks. This has beneficial effects in terms of bioavailability, drug metabolism, and pharmacodynamics. Drugs where these ideas have been established include bronchodilators, glucocorticoids, and nonsteroidal anti-inflammatory drugs.[16] Introduced recently, Bromocriptine, an oral antidiabetic drug for use as adjunct to diet and exercise in type-2 diabetics, is claimed to work by correcting the disrupted circadian rhythm.[17]

In view of these exciting recent developments, one can expect that in the near future there will be an even greater understanding of biological clocks. This should help in the development of many more clinical and therapeutic strategies in areas that were thought to be uninfluenced by fundamental and inherent oscillatory phenomenon that have their origin in the way that primordial life developed.

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How to cite this article: Apte CV. Biological clocks: The coming of age. Int J App Basic Med Res 2012;2:1-2.